Research

Impact of body mass index on efficacy and safety of ticagrelor versus clopidogrel in patients with minor stroke or transient ischemic attack

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Abstract

Background: Body mass index (BMI) may affect the response to platelet $P2Y_{12}$ receptor inhibitors. We aimed to explore whether BMI influenced the efficacy and safety of ticagrelor and clopidogrel for secondary prevention of minor ischemic stroke or transient ischemic attack (TIA) among patients enrolled in the CHANCE-2 (Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II) trial.

Methods: In a multicentre, randomized, double-blind, placebo-controlled trial, conducted in China, we randomized patients with minor stroke or TIA who carried the *CYP2C19* loss-of-function allele to receive either ticagrelor–acetylsalicylic acid (ASA) or clopidogrel–ASA. We classified patients into obese (BMI ≥ 28) or nonobese (BMI < 28) groups. The primary efficacy outcome was stroke within 90 days, and the primary safety outcome was severe or moderate bleeding within 90 days.

Results: Among 6412 patients, 876 were classified as obese and 5536 were classified as nonobese. Compared with clopidogrel–ASA, ticagrelor–ASA was associated with a significantly lower rate of stroke within 90 days among patients with obesity (25 [5.4%] v. 47 [11.3%]; hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.30–0.87), but not among those in the nonobese group (166 [6.0%] v. 196 [7.0%]; HR 0.84, 95% CI 0.69–1.04) The interaction of treatment and BMI group was significant (p for interaction = 0.04). We did not observe any difference by BMI group in rates of severe or moderate bleeding (9 [0.3%] v. 10 [0.4%] in the nonobese group; 0 [0.0%] v. 1 [0.2%] in the obese group; p for interaction = 0.99).

Interpretation: In this secondary analysis of a randomized controlled trial involving patients with minor ischemic stroke or TIA, compared with clopidogrel–ASA, patients with obesity received more clinical benefit from ticagrelor–ASA therapy than those without obesity. **Trial registration:** Clinical trials.gov, no. NCT04078737.

Trials of antithrombotic drugs have established the efficacy of dual antiplatelet therapy with clopidogrel and acetylsalicylic acid (ASA) or with ticagrelor and ASA for treating patients with minor ischemic stroke or transient ischemic attack (TIA).[1–4] However, different factors can influence the efficacy of antiplatelet therapy,[5,6] resulting in variability in patients' responses to antiplatelet drugs.[7–9] Thus, some patients are at higher risk of thrombotic events and recurrent strokes.[9] Early identification and management of these patients is of great importance for secondary prevention of stroke.

Obesity affects people globally,[10] and people with obesity have a high risk for stroke.[11] Patients with obesity display higher platelet reactivity and lower response to antiplatelet agents, compared with people without obesity.[12] Previous studies have reported an interaction between obesity and antiplatelet agents,[13–16] and body mass index (BMI) may affect the efficacy of platelet $P2Y_{12}$ receptor inhibitors.[15,17,18] Patients receiving clopidogrel are at increased risk of high residual platelet reactivity if their BMI is elevated.[19] Post hoc analysis of the Clopidogrel in High-Risk Patients With ASA in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trial found that clopidogrel–ASA therapy did not benefit patients with obesity, regardless of their *CYP2C19* loss-of-function allele status.[20]

Ticagrelor is more efficacious than clopidogrel in decreasing the risk of ischemic events among patients with acute coronary

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syndrome.[21] The Ticagrelor or Clopidogrel with Aspirin in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE-2) trial only enrolled patients with minor ischemic stroke or TIA who carried *CYP2C19* loss-of-function alleles and found that ticagrelor–ASA therapy was better than clopidogrel–ASA therapy in reducing the risk of stroke.[4] A lower proportion of patients with minor ischemic stroke or TIA treated with ticagrelor show high residual platelet reactivity than patients treated with clopidogrel, particularly among carriers of *CYP2C19* loss-of-function alleles.[22] However, more evidence is needed regarding the influence of BMI on the efficacy and safety of ticagrelor compared with clopidogrel among patients with stroke who carry *CYP2C19* loss-of-function alleles.

In this secondary analysis of the CHANCE-2 trial, we aimed to compare the efficacy and safety of ticagrelor–ASA and clopidogrel–ASA among patients with minor ischemic stroke or TIA who carry *CYP2C19* loss-of-function alleles, stratified by BMI.

Methods

Study population

The CHANCE-2 trial was a randomized, double-blind, placebo-controlled, multicentre trial, conducted at 202 centres in China from Sept. 23, 2019, to Mar. 22, 2021. The protocol of this trial (including rationale, design and methods) has been previously described in detail.[4] Included patients were aged 40 years or older, had either had an acute minor ischemic stroke (defined by a National Institutes of Health Stroke Score ≤ 3) or a high-risk TIA (defined by a ABCD^2 [age, blood pressure, clinical features, duration and presence or absence of diabetes mellitus] score ≥ 4), carried a *CYP2C19* loss-of-function allele and could start the study drug treatment within 24 hours of symptom onset. Patients who had received intravenous thrombolytic therapy or mechanical thrombectomy, or planned surgery or interventional treatment requiring cessation of the trial drug were excluded. Additional exclusion criteria were moderate-to-severe disability (modified Rankin Scale [mRS] of 3–5; overall range 0–6, with higher scores indicating greater disability), a history of intracranial hemorrhage or amyloid angiopathy, treatment with dual antiplatelet therapy within 72 hours before randomization, current treatment with heparin therapy or oral anticoagulation (presumed cardiac source of embolus, such as atrial fibrillation, prosthetic cardiac valve and known or suspected endocarditis) or a contraindication to ASA, ticagrelor or clopidogrel.

Point-of-care genotyping

After obtaining informed consent for screening, a GMEX point-of-care genotyping system was used to implement rapid genotyping for 3 single nucleotide polymorphisms (*CYP2C19*2*, *CYP2C19*3* and *CYP2C19*17*). Patients with at least 1 loss-of-function allele (**2* or **3*) were considered to carry loss-of-function alleles and were enrolled in the trial. Patients with 2 loss-of-function alleles (**2/*2*, **2/*3* or **3/*3*) were classified as poor metabolizers, and those with 1 loss-of-function allele (**1/*2* or **1/*3*) were classified as intermediate metabolizers. *CYP2C19*17* increases the concentration of effective metabolite in vivo. Patients carrying at least 1 **17* allele (**1/*17* or **17/*17*) were classified as an as ultra-rapid metabolizer and not considered to carry loss-of-function alleles.

Randomization and treatment

Patients were randomly assigned in a 1:1 ratio within 24 hours after symptom onset to receive 90 days of ticagrelor (180 mg loading dose on day 1, followed by 90 mg twice daily on days 2–90, plus placebo clopidogrel) or clopidogrel (300 mg loading dose on day 1, followed by 75 mg/d on days 2–90, plus placebo ticagrelor). All patients received 21 days of ASA (75–300 mg loading dose on day 1, followed by 75 mg/d for 21 days). At the end of the 90 days of treatment with the study drug, the treating physician decided what antiplatelet agents to prescribe.

Body mass index

Trained staff measured height using a stadiometer and weight using class III weighing equipment; patients wore light clothing and no shoes. Patient BMI was calculated as weight (kg) divided by height (m) in metres squared (kg/m^2). We classified patients into obese (BMI ≥ 28) or nonobese (including BMI < 24 and 24–28) groups according to the criteria of the Chinese Bureau of Disease Control in the Ministry of Health.[23,24] Because disease-related, ethnicity-specific BMI cut-offs for obesity are different for people of Chinese descent (26.9),[25] and the guideline of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society recommends starting intervention when the BMI is 27 or higher in patients with comorbidities,[26] we grouped patients by BMI (< 27 v. ≥ 27) for sensitivity analyses.

Outcomes

The primary efficacy outcome was an ischemic or hemorrhagic stroke within 90 days. The secondary efficacy outcomes included ischemic stroke within 90 days, new stroke within 30 days, a vascular event (a composite of stroke, TIA, myocardial infarction or vascular death) within 90 days, disabling stroke (mRS ≥ 2) within 90 days and severity of stroke or TIA within 90 days (measured on a 6-level ordinal scale as fatal stroke, severe stroke [mRS 4–5], moderate stroke [mRS 2–3], mild stroke [mRS 0–1], TIA or no stroke or TIA).[27]

The primary safety outcome was severe or moderate bleeding within 90 days, defined using the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.[28] Secondary safety outcomes were any bleeding, mild bleeding and death within 90 days.

Statistical analysis

We expressed continuous variables as medians with interquartile ranges, and categorical variables as frequencies with percentages. We constructed cumulative event curves for the primary outcome using the Kaplan–Meier method, and used Cox proportional hazards regression analyses with study centres as a random effect to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes during the 90-day follow-up period. We evaluated the effect of continuous BMI on the efficacy

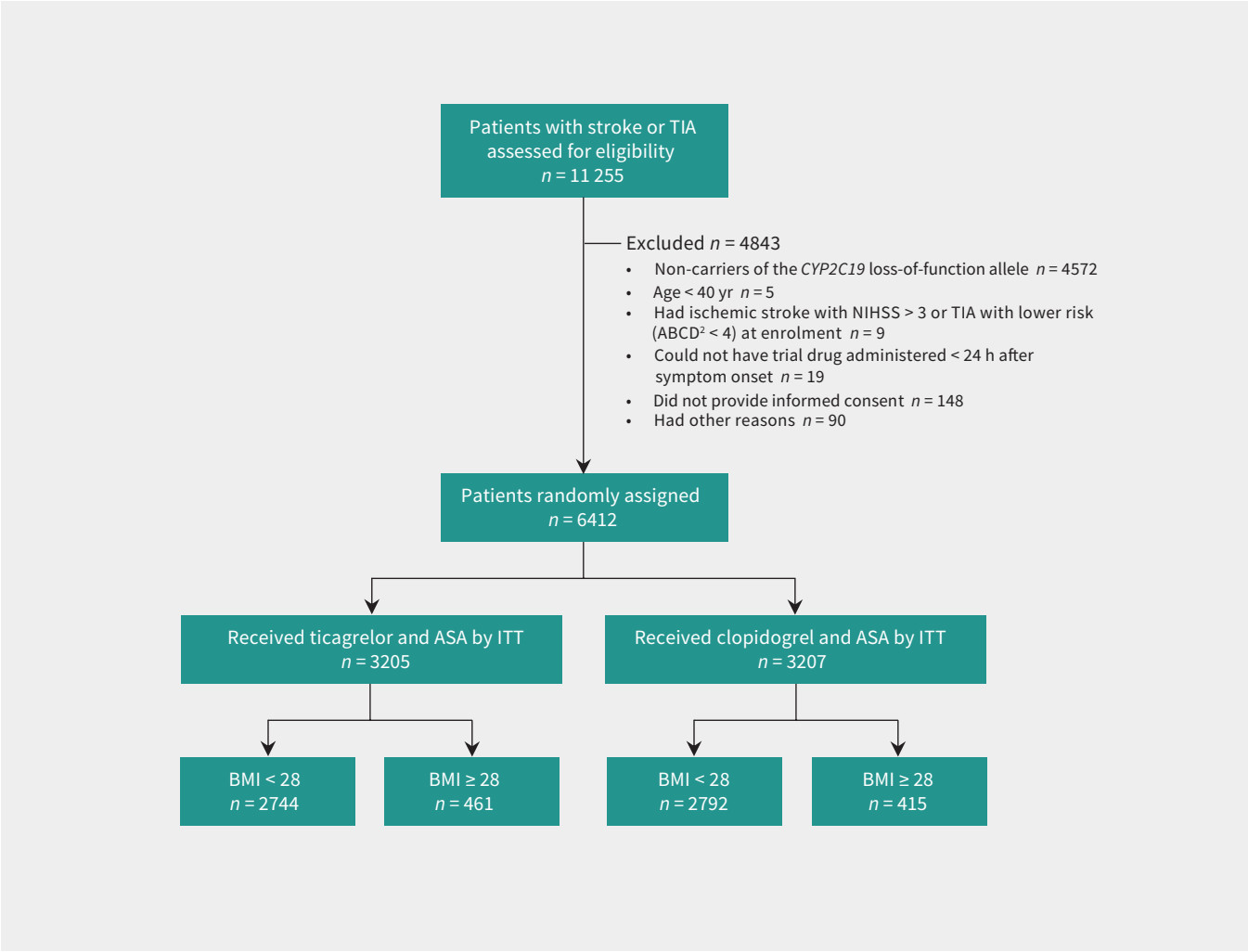

Figure 1: Flow chart of this study. Note: ABCD² = age, blood pressure, clinical features, duration of TIA and presence or absence of diabetes; ASA = acetylsalicylic acid; BMI = body mass index; ITT = intention to treat; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

of treatment, assuming a linear relationship.[29] If multiple events of the same type occurred, we calculated the time to event as the time to first event. We assessed the proportional hazards assumption by testing the significance of the interaction term between treatment groups and time, and it was not violated in any of the Cox models. We evaluated the interaction between treatment groups and BMI categories by adding this interaction term into the models. Given the small number of safety events, we used exact Cox regression to estimate the HR, adding a treatment by BMI interaction term into the model.[30] Because we prespecified stroke within 90 days as the primary outcome, we considered the secondary outcomes to be exploratory and hypothesis generating; we did not adjust for multiple testing. We performed all statistical analyses with SAS statistical software, version 9.4 (SAS Institute). All tests were 2-sided, and we considered *p* values of less than 0.05 to be statistically significant.

Ethics approval

The trial was approved by the ethics committees at Beijing Tiantan Hospital (KY2019–035–02) and at each participating centre, and was registered at ClinicalTrials.gov (NCT04078737). All participants or their representatives signed the written informed consent before enrolment.

Results

Of the 6412 patients enrolled in the CHANCE-2 trial, 3205 patients were randomized to the ticagrelor–ASA group and 3207 patients were randomized to the clopidogrel–ASA group; 876 (13.7%) were classified as obese and 5536 (86.3%) were classified as nonobese (Figure 1). The baseline clinical characteristics were well balanced between arms within BMI groups (Table 1). Similar results were found in the sensitivity analysis (Appendix 1, Table S1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230262/tab-related-content). After 90 days of treatment with the study drug, secondary prevention was prescribed by the treating physician; 6119 (95.4%) of patients received lipid-lowering drugs, 1766 (27.5%) received hypoglycemic drugs and 3602 (56.2%) received antihypertensive drugs. These drugs were prescribed with similar frequency in the clopidogrel and ticagrelor groups for patients with or without obesity.

Table 1: Baseline patient characteristics

Characteristic	Overall *n* = 6412	Nonobese (BMI < 28)		Obese (BMI ≥ 28)	
		No. (%) of patients on ticagrelor–ASA *n* = 2744	No. (%) of patients on clopidogrel–ASA *n* = 2792	No. (%) of patients on ticagrelor–ASA *n* = 461	No. (%) of patients on clopidogrel–ASA *n* = 415
Age, yr, median (IQR)	64.8 (57.0–71.4)	65.3 (57.4–72.2)	65.0 (57.4–71.4)	62.3 (54.3–69.2)	61.7 (53.4–69.4)
Sex, female	2170 (33.8)	913 (33.3)	895 (32.1)	177 (38.4)	185 (44.6)
Han ethnicity	6282 (98.0)	2688 (98.0)	2731 (97.8)	456 (98.9)	407 (98.1)
Systolic blood pressure, mm Hg, median (IQR)	148 (136–162)	148 (136–162)	148 (135–161)	150 (138–161)	150 (140–162)
Diastolic blood pressure, mm Hg, median (IQR)	86 (80–95)	86 (80–95)	86 (80–94)	89 (80–96)	90 (80–100)
Medical history					
Hypertension	3955 (61.7)	1648 (60.1)	1676 (60.0)	328 (71.1)	303 (73.0)
Diabetes mellitus	1563 (24.4)	685 (25.0)	632 (22.6)	123 (26.7)	123 (29.6)
Dyslipidemia	614 (9.6)	265 (9.7)	253 (9.1)	58 (12.6)	38 (9.2)
Previous ischemic stroke	1350 (21.1)	577 (21.0)	593 (21.2)	92 (20.0)	88 (21.2)
Previous TIA	88 (1.4)	36 (1.3)	39 (1.4)	10 (2.2)	3 (0.7)
Myocardial infarction	96 (1.5)	47 (1.7)	34 (1.2)	7 (1.5)	8 (1.9)
Current smoker	1981 (30.9)	865 (31.5)	873 (31.3)	130 (28.2)	113 (27.2)
Type of *CYP2C19* loss-of-function allele carrier†					
Intermediate metabolizers	5001 (78)	2138 (77.9)	2194 (78.6)	348 (75.5)	321 (77.3)
Poor metabolizers	1411 (22)	606 (22.1)	598 (21.4)	113 (24.5)	94 (22.7)
Median time from symptom onset to randomization					
< 12 h	2626 (41.0)	1142 (41.6)	1137 (40.7)	186 (40.4)	161 (38.8)
≥ 12 h	3786 (59.0)	1602 (58.4)	1655 (59.3)	275 (59.6)	254 (61.2)
Qualifying event					
Ischemic stroke	5158 (80.4)	2218 (80.8)	2249 (80.6)	359 (77.9)	332 (80.0)
TIA	1254 (19.6)	526 (19.2)	543 (19.4)	102 (22.1)	83 (20.0)
NIHSS score among patients with ischemic stroke, median (IQR)‡	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
ABCD^2 score among patients with TIA, median (IQR)§	4 (4–5)	5 (4–5)	5 (4–5)	4 (4–5)	4 (4–5)
Previous medication¶					
Antiplatelet agents	748 (11.7)	317 (11.6)	309 (11.1)	68 (14.8)	54 (13.0)
Lipid-lowering agents	499 (7.8)	210 (7.7)	210 (7.5)	48 (10.4)	31 (7.5)
TOAST type					
Large-artery atherosclerosis	2997 (54.4)	1281 (54.1)	1330 (55.3)	209 (54.0)	177 (50.6)
Small-artery occlusion	24 (0.4)	13 (0.5)	10 (0.4)	1 (0.3)	0 (0.0)
Cardioembolism	2288 (41.5)	981 (41.4)	988 (41.0)	166 (42.9)	153 (43.7)
Other determined cause	67 (1.2)	27 (1.1)	32 (1.3)	3 (0.8)	5 (1.4)
Undetermined cause	137 (2.5)	67 (2.8)	47 (2.0)	8 (2.1)	15 (4.3)
Symptomatic ICAS	2385 (40.3)	1022 (40.2)	1007 (39.3)	185 (43.4)	171 (43.8)
Symptomatic ECAS	524 (8.9)	243 (9.6)	216 (8.4)	32 (7.5)	33 (8.5)

Note: ABCD^2 = age, blood pressure, clinical features, duration of TIA and presence or absence of diabetes; ASA = acetylsalicylic acid; BMI = body mass index; ECAS = extracranial artery stenosis; ICAS = intracranial artery stenosis; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; TIA = transient ischemic attack.
*Unless indicated otherwise.
†Patients with 1 *CYP2C19*2* or *CYP2C19*3* allele were considered intermediate metabolizers; those with a combination of 2 *CYP2C19*2* or *CYP2C19*3* alleles were considered poor metabolizers.
‡NIHSS scores range from 0–42, with higher scores indicating more severe stroke.
§The ABCD^2 score assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA and presence or absence of diabetes. Scores range from 0–7 and higher scores indicate greater risk.
¶Medication within 1 month before symptom onset.

Efficacy outcomes

As BMI increased, the risk of stroke within 90 days decreased among patients receiving ticagrelor–ASA therapy compared with those receiving clopidogrel–ASA (Figure 2). When modelling BMI as a continuous variable, each 5 unit increase in BMI was associated with a 17.98% (95% CI 17.97%–18.00%) decrease in the HR of 90-day stroke for ticagrelor–ASA, compared with clopidogrel–ASA. Ticagrelor–ASA was associated with a significantly lower rate of

stroke within 90 days among patients with obesity (HR 0.51, 95% CI 0.30–0.87), but not among patients in the nonobese group (HR 0.84, 95% CI 0.69–1.04) (Table 2 and Figure 3). The interaction of treatment group and BMI group was significant ($p = 0.04$). Similar results were found for the secondary efficacy outcomes of ischemic stroke (p for interaction = 0.04), vascular event within 90 days (p for interaction = 0.04) and ordinal stroke or TIA within 90 days (p for interaction = 0.02). In addition, we observed a similar trend that was almost statistically significant for ischemic stroke within 90 days (p for interaction = 0.08). Ticagrelor–ASA showed similar benefits for patients with obesity after stratifying into 3 BMI groups (< 24, 24–28 and > 28), but the interaction of BMI group and treatment group was not statistically significant (Appendix 1, Table S4). Sensitivity analyses showed similar results (Appendix 1, Table S2 and Appendix 2, Figure S1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.230262/tab-related-content).

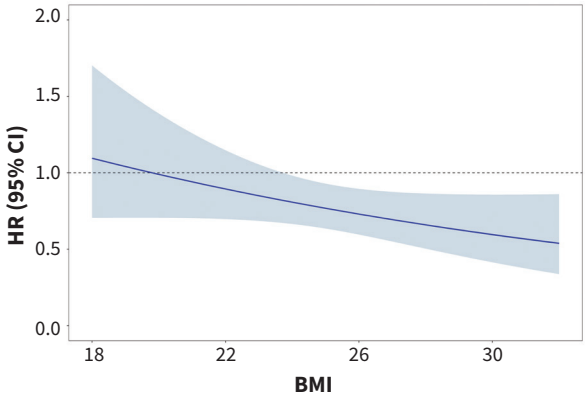

Figure 2: Influence of body mass index (BMI) on the effect of ticagrelor–acetylsalicylic acid (ASA) versus clopidogrel–ASA for stroke within 90 days among patients with minor stroke or transient ischemic attack who carried a *CYP2C19* loss-of-function allele. Shaded area represents 95% confidence intervals (CIs). Note: HR = hazard ratio.

Safety outcomes

We did not observe a statistically significant difference in severe or moderate bleeding among patients in the 2 BMI groups (0.3% for patients on ticagrelor–ASA v. 0.4% for patients on clopidogrel–ASA in the nonobese group; 0.0% for patients on ticagrelor–ASA v. 0.2% for patients on clopidogrel–ASA in the obese group; p for interaction = 0.99) (Table 3). Similarly, obesity status did not alter the risk of other safety outcomes (Table 3). Sensitivity analyses showed similar results (Appendix 1, Table S3).

Table 2: Efficacy outcomes of ticagrelor–acetylsalicylic acid (ASA) and clopidogrel–ASA treatment, stratified by body mass index (BMI)

	Nonobese (BMI < 28)			Obese (BMI ≥ 28)			
Outcome	No. (%) of patients on ticagrelor–ASA* $n = 2744$	No. (%) of patients on clopidogrel–ASA* $n = 2792$	HR or OR† (95% CI)	No. (%) of patients on ticagrelor–ASA* $n = 461$	No. (%) of patients on clopidogrel–ASA* $n = 415$	HR or OR† (95% CI)	p interaction
Primary outcome							
Stroke	166 (6.0)	196 (7.0)	0.84 (0.69–1.04)	25 (5.4)	47 (11.3)	0.51 (0.30–0.87)	0.04
Secondary outcome							
Ischemic stroke	164 (6.0)	192 (6.9)	0.85 (0.69–1.05)	25 (5.4)	46 (11.1)	0.51 (0.30–0.89)	0.04
Stroke within 30 d	139 (5.1)	171 (6.1)	0.81 (0.65–1.01)	17 (3.7)	34 (8.2)	0.46 (0.24–0.87)	0.08
Vascular event‡	198 (7.2)	237 (8.5)	0.83 (0.69–1.01)	31 (6.7)	56 (13.5)	0.54 (0.33–0.87)	0.04
Stroke with any disability§	83 (3.0)	71 (2.5)	1.16 (0.84–1.59)	14 (3.0)	21 (5.1)	0.74 (0.36–1.52)	0.08
Ordinal stroke or TIA¶			0.86 (0.70–1.05)			0.48 (0.30–0.77)	0.02
No stroke or TIA	2550 (92.9)	2563 (91.8)		430 (93.3)	361 (87.0)		
TIA	28 (1.0)	33 (1.2)		6 (1.3)	7 (1.7)		
Mild stroke (mRS 0–1)	83 (3.0)	125 (4.5)		11 (2.4)	26 (6.3)		
Moderate stroke (mRS 2–3)	53 (1.9)	48 (1.7)		10 (2.2)	15 (3.6)		
Severe stroke (mRS 4–5)	26 (0.9)	16 (0.6)		4 (0.9)	5 (1.2)		
Fatal stroke (mRS 6)	4 (0.1)	7 (0.3)		0 (0.0)	1 (0.2)		

Note: CI = confidence interval, HR = hazard ratio, mRS = modified Rankin Scale, OR = odds ratio, TIA = transient ischemic attack.
*Event rates for ordinal stroke or TIA are raw estimates, whereas event rates for other outcomes are Kaplan–Meier estimates of the percentage of patients with events at 90 days.
†Hazard ratios for all outcomes except for ordinal stroke or TIA.
‡Vascular events were a composite of ischemic stroke, hemorrhagic stroke, TIA, myocardial infarction and vascular death.
§A stroke was defined as disabling if the patient had a mRS score of greater than 1 (indicating death or any degree of disability).
¶Severity measured using a 6-level ordered categorical scale that incorporated stroke or TIA events and mRS score at 3 months.

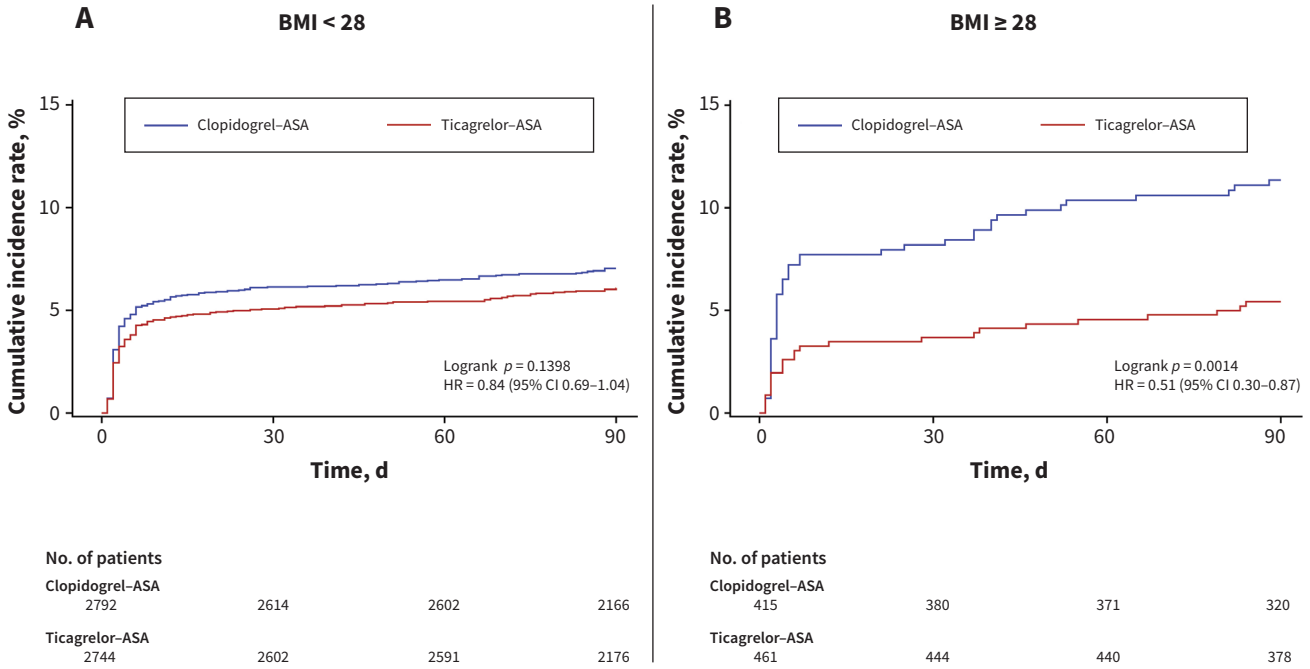

Figure 3: Kaplan–Meier plots of stroke among patients treated with either ticagrelor–acetylsalicylic acid (ASA) or clopidogrel–ASA, stratified by body mass index (BMI) (A) less than 28 or (B) 28 or higher. Note: CI = confidence interval; HR = hazard ratio.

Table 3: Safety outcomes of ticagrelor–acetylsalicylic acid (ASA) and clopidogrel–ASA treatment, stratified by body mass index (BMI)

	Nonobese (BMI < 28)			Obese (BMI ≥ 28)			
Outcome	No. (%) of patients on ticagrelor–ASA* *n* = 2744	No. (%) of patients on clopidogrel–ASA* *n* = 2792	HR (95% CI)	No. (%) of patients on ticagrelor–ASA* *n* = 461	No. (%) of patients on clopidogrel–ASA* *n* = 415	HR (95% CI)	*p* interaction
Primary safety outcome							
Severe or moderate bleeding†	9 (0.3)	10 (0.4)	0.91 (0.37–2.24)	0 (0.0)	1 (0.2)	NA	0.99
Fatal bleeding	3 (0.1)	3 (0.1)	1.00 (0.20–4.94)	0 (0.0)	0 (0.0)	NA	1.0
Intracranial hemorrhage	3 (0.1)	5 (0.2)	0.57 (0.14–2.41)	0 (0.0)	1 (0.2)	NA	0.99
Secondary safety outcome							
Any bleeding	146 (5.3)	70 (2.5)	2.19 (1.64–2.93)	24 (5.2)	10 (2.4)	2.65 (1.14–6.19)	0.94
Mild bleeding	137 (5.0)	60 (2.1)	2.43 (1.78–3.30)	24 (5.2)	9 (2.2)	2.89 (1.19–7.00)	0.95
Death	9 (0.3)	16 (0.6)	0.56 (0.25–1.27)	0 (0.0)	2 (0.5)	NA	0.99

Note: BMI = body mass index, CI = confidence interval, HR = hazard ratio, NA = not applicable, OR = odds ratio.
*Event rates are Kaplan–Meier estimates of the percentage of patients with events at 90 days.
†Severe or moderate bleeding and mild bleeding were defined according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria.

Interpretation

In this secondary analysis of the CHANCE-2 trial, BMI modified the efficacy of ticagrelor–ASA therapy, compared with clopidogrel–ASA therapy. Ticagrelor–ASA therapy was associated with a lower risk of stroke among patients with obesity, but not among patients in the nonobese group when we analyzed BMI categorically (with a BMI cut-off of 28) or as a continuous variable. Our findings suggest that ticagrelor–ASA therapy could benefit carriers of *CYP2C19* loss-of-function alleles with obesity in reducing the risk of stroke, compared with clopidogrel–ASA therapy.

Studies have reported that the pharmacokinetic and pharmacodynamic properties of $P2Y_{12}$ inhibitors are altered among patients with obesity.[31,32] A secondary analysis of the CHANCE

study suggested that clopidogrel did not decrease the risk of stroke among patients with a minor ischemic stroke or TIA who were overweight or obese.[20] A study of patients with coronary artery disease showed that patients with a weight of 60 kg or greater had lower exposure to the active metabolite of clopidogrel, compared with those whose weight was less than 60 kg;[32] a single, high loading dose of clopidogrel (600 mg) did not inhibit platelet aggregation among patients who were overweight or obese, although the same dose was effective among patients with normal weight.[33]

Conversely, although BMI affects platelet reactivity during ticagrelor therapy,[6,34] studies have shown that BMI may not affect the efficacy and safety of ticagrelor. Two randomized controlled trials (RCTs) compared the effect of BMI on ticagrelor monotherapy and found that, compared with ticagrelor–ASA, BMI category did not affect the efficacy and safety of ticagrelor monotherapy.[35,36] Another RCT found a similar treatment effect of ticagrelor monotherapy versus standard dual antiplatelet therapy with ticagrelor–ASA across BMI groups.[37] Also, the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial found that, although BMI did not affect the efficacy of ticagrelor or clopidogrel, treatment with ticagrelor reduced the frequency of ischemic events compared with clopidogrel among patients who weighed more than the median value for their sex.[21]

Ticagrelor is a direct-acting inhibitor of the $P2Y_{12}$ receptor, with a wide therapeutic window, and does not require transformation to active metabolites, while clopidogrel relies on cytochrome P450 3A4 to transform into an active form in the liver.[38,39] The activity of metabolites is reduced among people who are overweight or obese, perhaps because of the influence of higher levels of free fatty acids on hepatocytes.[40] Body mass index and genotyping are parts of the ABCD-GENE (Age, Body Mass Index, Chronic Kidney Disease, Diabetes and Genotyping) risk score, which identifies patients with high residual platelet reactivity on clopidogrel therapy.[5] In a post hoc analysis of the CHANCE study, we found that the efficacy of clopidogrel–ASA therapy was decreased among patients with minor ischemic stroke or TIA and a higher ABCD-GENE risk score.[41]

Consistent with the PLATO trial, in this study involving patients with minor ischemic stroke or TIA carrying a *CYP2C19* loss-of-function allele, we found that ticagrelor–ASA therapy was more efficacious than clopidogrel–ASA therapy among patients with obesity and that ticagrelor–ASA therapy did not increase the risk of severe or moderate bleeding although the risk of minor bleeding was increased.[19]

Limitations

The correlation between fat mass and BMI is modest; thus, other anthropometric measurements should be taken in consideration in defining obesity.[42] However, BMI is the easiest and most frequently used measure of obesity and has been recommended for the analyses of data from antithrombotic trials.[42] This study was a secondary analysis, which could increase the risk of a type I error. The cut-off value for BMI was not prespecified but was determined by its clinical interpretation; however, modelling BMI as a continuous variable also found that the benefit of ticagrelor was increased among patients with higher BMI, compared with clopidogrel. The effect modification of BMI should be confirmed in future studies. Future studies are also needed to explore the influence of BMI on longer-term outcomes; we are planning an analysis to study the longer-term effect of ticagrelor versus clopidogrel among patients with minor ischemic stroke or TIA who carry the *CYP2C19* loss-of-function allele, stratified by BMI. Finally, our findings need to be confirmed in non-Han populations.

Conclusion

Body mass index influences the efficacy of ticagrelor–ASA versus clopidogrel–ASA among patients with minor ischemic stroke or TIA who carry a *CYP2C19* loss-of-function allele. Clopidogrel appears to lose its efficacy among patients with obesity. Patients with obesity appear to derive clinical benefit from ticagrelor–ASA therapy without increasing risk of moderate or severe bleeding after minor ischemic stroke or TIA.

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